

REMARKS

Claims 1, 2, 9-14 and 21-36 are pending. Claims 1, 2, and 9-20 were withdrawn from consideration. The pending claims are free of the prior art. A period has been inserted at the end of Claim 21. Claim 36 has been amended to replace the word “preventing” with “alleviating”. Support for this change is found in the specification on page 8, line 26. Accordingly, the Applicants do not believe that any new matter has been added.

The Applicants thank Examiner Jones for the courteous and helpful discussion of November 12, 2004. It was suggested that the Applicants demonstrate a nexus between calcium channel potentiation and treatment of brain diseases or disorders. It was also suggested that the word “preventing” be deleted from Claim 36.

The Applicants attach herewith copies of scientific journal articles demonstrating the role of N-type calcium channel currents in fine tuning of neurotransmitter release as well as the ability of agents which modulate N-type calcium channel current to treat dementia and other diseases and disorders such as schizophrenia, depression and stroke. Claim 36 has been amended to remove the word “preventing”. Accordingly, favorable consideration is now respectfully requested.

Rejection – 35 U.S.C. § 112, first paragraph

Claims 21-36 were rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate enablement for treatment of brain disorders. The Applicants thank Examiner for acknowledging that the claims are enabling for potentiating N-type calcium channel activity. The remaining concern was that the Applicants had not demonstrated any nexus or interrelationship between the potentiation of an N-type calcium channel and the treatment of a brain disorder or disease.

The Applicants now elaborate on the nexus between potentiating N-type calcium channel activity and treatment of brain disorders and diseases. Initially, the Applicants point out descriptive support in the specification for treatment of brain disorders and diseases by potentiating N-type calcium channel activity. For example, the treatment of brain disorders by potentiating N-type calcium channel activity is described in the specification on page 1, lines 5-11, page 3, lines 13-16, and page 4, lines 4-15 and page 8, lines 25-26. The Applicants respectfully point out that the Office has the initial burden of showing that one of ordinary skill in the art would reasonably doubt the asserted utility (and thus enablement) of treating brain disorders or diseases by potentiating N-type calcium channel activity, see MPEP 2164.07(I)(B). Moreover, a specification that contains a teaching of the manner and process of making and using an invention which correspond in scope to those sought to be patented must be taken as being in compliance with 35 U.S.C. 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained in the specification.

Clearly the specification teaches how to make and use the claimed methods as required by 35 U.S.C. 112, first paragraph: by administering an agent which potentiates N-type calcium channel activity. The Office has not met this initial burden of establishing why potentiating N-type calcium channel activity would **NOT** treat a brain disorder or disease.

Notwithstanding the above, the Office has indicated that methods of potentiating N-type calcium channels are enabled, but has requested that the Applicant demonstrate a nexus between potentiation of N-type calcium channels and treatment of brain disorders and diseases. While the Official Action which refers to the Wands factors suggests that undue experimentation would be required to practice the invention, establishing a nexus between potentiation of N-type calcium channel activity and treatment of brain disease and disorders

appears to be the critical issue<sup>1</sup>. Moreover, by establishing this nexus, the Applicants show a common neurological mechanism for treating a variety of brain disorders and diseases and thus address concerns posed in the Official Action.

As indicated in the specification and as substantiated by the references discussed below, agents which potentiate N-type calcium channel activity have been shown to produce biologically significant effects on the nervous system and the administration of N-type calcium channel potentiators has actually been shown to treat brain disorders and diseases. Thus, they have credible utility.

A. Catterall, Cell Calcium 2/6:307 (1998), discloses that N-type calcium channels play a key role in neurological function. Thus, potentiation of these key functions would be expected to remedy functional deficits associated with particular brain diseases.

B. Cooper et al., J. Biol. Chem. 275:40777, indicates that modulation of N-type calcium current is a factor in the fine tuning of neurotransmitter release, see e.g., abstract. One with ordinary skill in the art would recognize the utility of modulating neurotransmitter release, for example, the value of increasing the levels of neurotransmitters in brain disorders in patients exhibiting neurotransmitter deficits and the value of decreasing or balancing neurotransmitter levels in patients having other brain diseases or disorders.

C. Wang et al., J. Pharmacol. Exp. Therap. 308 :120, exemplifies an agent which modulates N-type calcium channel current and which provides significant anti-dementia effects, see abstract. This document clearly shows the nexus between an N-type calcium channel potentiator and treatment of brain disorders such as dementia and Alzheimer's disease. The compound of Wang et al. (FK-906) falls within formula (I) and is excluded

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<sup>1</sup> The Official Action indicates that the claimed method involves "administering the piperazinyl compounds of formula (I)", see page 4 (1). The Applicants note that compounds of formula (I) are excluded from the present claims.

from the present claims<sup>2</sup>. Nevertheless, Wang demonstrate the utility (and enablement) of agents which potentiate N-type calcium channel activity.

D. Marston et al., WO98/27930, disclose the treatment of brain disorders and diseases, such as schizophrenia, depression and stroke using the N-type calcium channel potentiator FK-906.

Based on the present specification, as well as on the prior art, the Applicants respectfully submit that the claimed methods directed to treatment of brain disorders using N-type calcium channel potentiators have credible utility (and thus enablement) for treating brain disorders and diseases. Therefore, this rejection may now be withdrawn.

#### CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. Early notification to that effect is earnestly solicited.

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<sup>2</sup> While Wang disclose FK-906, they do not disclose which the type of calcium channel (e.g., L-type, N-type, P-type, T-type, etc.) must be potentiated to treat brain disorders or diseases. The present inventors were the first to identify the value of potentiating N-type calcium channels, see e.g., the specification, page 3, lines 10-19. Wang do not disclose the N-type calcium channel potentiators encompassed by the present claims, nor provide any motivation for specifically potentiating N-type calcium channel activity.